

Claims

1. A composition comprising a selective serotonin reuptake inhibitor (SSRI) or analog thereof and a corticosteroid in amounts that together are sufficient *in vivo* to decrease proinflammatory cytokine secretion or production or to treat an immunoinflammatory disorder.

2. The composition of claim 1, wherein said SSRI is cericlamine, citalopram, clovoxamine, cyanodothiepin, dapoxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, indeloxazine, litoxetine, milnacipran, paroxetine, sertraline, tametraline, viqualine, or zimeldine.

3. The composition of claim 1, wherein said corticosteroid is prednisolone, cortisone, budesonide, dexamethasone, hydrocortisone, methylprednisolone, fluticasone, prednisone, triamcinolone, or diflorasone.

4. The composition of claim 1, wherein said SSRI is fluoxetine or paroxetine and said corticosteroid is prednisolone.

5. The composition of claim 1, wherein said SSRI or said corticosteroid is present in said composition in a low dosage.

6. The composition of claim 1, wherein said SSRI or said corticosteroid is present in said composition in a high dosage.

7. The composition of claim 1, further comprising an NSAID, COX-2 inhibitor, biologic, small molecule immunomodulator, DMARD, xanthine, anticholinergic compound, beta receptor agonist, bronchodilator, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid, or 5-amino salicylic acid.

8. The composition of claim 7, wherein said NSAID is ibuprofen, diclofenac, or naproxen.
9. The composition of claim 7, wherein said COX-2 inhibitor is rofecoxib, celecoxib, valdecoxib, or lumiracoxib.
10. The composition of claim 7, wherein said biologic is adalimumab, etanercept, or infliximab.
11. The composition of claim 7, wherein said DMARD is methotrexate or leflunomide.
12. The composition of claim 7, wherein said xanthine is theophylline.
13. The composition of claim 7, wherein said anticholinergic compound is ipratropium or tiotropium.
14. The composition of claim 7, wherein said beta receptor agonist is albuterol sulfate, bitolterol mesylate, epinephrine, formoterol fumarate, isoproterenol, levalbuterol hydrochloride, metaproterenol sulfate, pirbuterol scetate, salmeterol xinafoate, or terbutaline.
15. The composition of claim 7, wherein said non-steroidal calcineurin inhibitor is cyclosporine, tacrolimus, pimecrolimus, or ISAtx247.
16. The composition of claim 7, wherein said vitamin D analog is calcipotriene or calcipotriol.

17. The composition of claim 7, wherein said psoralen is methoxsalen.
18. The composition of claim 7, wherein said retinoid is acitretin or tazarotene.
19. The composition of claim 7, wherein said 5-amino salicylic acid is mesalamine, sulfasalazine, balsalazide disodium, or olsalazine sodium.
20. The composition of claim 1, wherein said composition is formulated for topical administration.
21. The composition of claim 1, wherein said small molecule immunomodulator is VX 702, SCIO 469, doramapimod, RO 30201195, SCIO 323, DPC 333, pranalcasan, mycophenolate, or merimepodib.
22. The composition of claim 1, wherein said SSRI analog is a serotonin, norepinephrine reuptake inhibitor (SNRI).
23. The composition of claim 22, wherein said SNRI is venlafaxine, duloxetine, or 4-(2-fluorophenyl)-6-methyl-2-piperazinothieno [2,3-d] pyrimidine.
24. The composition of claim 1, wherein said composition is formulated for systemic administration.
25. A method of decreasing proinflammatory cytokine secretion or production in a patient, said method comprising administering to the patient an SSRI or analog thereof and a corticosteroid simultaneously or within 14 days of each other in amounts sufficient *in vivo* to decrease proinflammatory cytokine secretion or production in said patient.

26. A method for treating a patient diagnosed with or at risk of developing an immunoinflammatory disorder, said method comprising administering to the patient an SSRI or analog thereof and a corticosteroid simultaneously or within 14 days of each other in amounts sufficient to treat said patient.

27. The method of claim 26, wherein said immunoinflammatory disorder is rheumatoid arthritis, Crohn's disease, ulcerative colitis, asthma, chronic obstructive pulmonary disease, polymyalgia rheumatica, giant cell arteritis, systemic lupus erythematosus, atopic dermatitis, multiple sclerosis, cirrhosis, myasthenia gravis, psoriasis, ankylosing spondylitis, or psoriatic arthritis.

28. The method of claim 26, wherein said SSRI is cericlamine, citalopram, clovoxamine, cyanodothiepin, dapoxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, indeloxazine, litoxetine, milnacipran, paroxetine, sertraline, tametraline, viqualine, or zimeldine.

29. The method of claim 26, wherein said SNRI is venlafaxine, duloxetine, or 4-(2-fluorophenyl)-6-methyl-2-piperazinothieno [2,3-d] pyrimidine.

30. The method of claim 26, wherein said corticosteroid is prednisolone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, fluticasone, prednisone, triamcinolone, or diflorasone.

31. The method of claim 26, further comprising administering to said patient an NSAID, COX-2 inhibitor, biologic, small molecule immunomodulator, DMARD, xanthine, anticholinergic compound, beta receptor agonist, bronchodilator, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid, and 5-amino salicylic acid.

32. The method of claim 31, wherein said NSAID is ibuprofen, diclofenac, or naproxen.

33. The method of claim 31, wherein said COX-2 inhibitor is rofecoxib, celecoxib, valdecoxib, or lumiracoxib.

34. The method of claim 31, wherein said biologic is adalimumab, etanercept, or infliximab.

35. The method of claim 31, wherein said DMARD is methotrexate or leflunomide.

36. The method of claim 31, wherein said xanthine is theophylline.

37. The method of claim 31, wherein said anticholinergic compound is ipratropium or tiotropium.

38. The method of claim 31, wherein said beta receptor agonist is albuterol sulfate, bitolterol mesylate, epinephrine, formoterol fumarate, isoproterenol, levalbuterol hydrochloride, metaproterenol sulfate, pirbuterol scetate, salmeterol xinafoate, or terbutaline.

39. The method of claim 31, wherein said non-steroidal calcineurin inhibitor is cyclosporine, tacrolimus, pimecrolimus, or ISAtx247.

40. The method of claim 31, wherein said vitamin D analog is calcipotriene or calcipotriol.

41. The method of claim 31, wherein said psoralen is methoxsalen.

42. The method of claim 31, wherein said retinoid is acitretin or tazarotene.
43. The method of claim 31, wherein said 5-amino salicylic acid is mesalamine, sulfasalazine, balsalazide disodium, or olsalazine sodium.
44. The method of claim 26, wherein said small molecule immunomodulator is VX 702, SCIO 469, doramapimod, RO 30201195, SCIO 323, DPC 333, pranalcasan, mycophenolate, or merimepodib.
45. The method of claim 26, wherein said SSRI or said corticosteroid is administered in a low dosage.
46. The method of claim 26, wherein said SSRI or said corticosteroid is administered in a high dosage.
47. The method of claim 26, wherein said SSRI and said corticosteroid are administered within 10 days of each other.
48. The method of claim 47, wherein said SSRI and said corticosteroid are administered within five days of each other.
49. The method of claim 48, wherein said SSRI and said corticosteroid are administered within twenty-four hours of each other.
50. The method of claim 49, wherein said SSRI and said corticosteroid are administered simultaneously.

51. A composition comprising an SSRI or an analog thereof and a glucocorticoid receptor modulator in amounts that together are sufficient to decrease proinflammatory cytokine secretion or production.

52. The composition of claim 51, wherein said SSRI is cericlamine, citalopram, clovoxamine, cyanodothiepin, dapoxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, indeloxazine, litoxetine, milnacipran, paroxetine, sertraline, tametraline, viqualine, or zimeldine.

53. The composition of claim 51, further comprising a compound selected from the group consisting of a NSAID, COX-2 inhibitor, biologic, DMARD, xanthine, anticholinergic compound, beta receptor agonist, bronchodilator, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid, and 5-amino salicylic acid.

54. The composition of claim 51, wherein said SSRI analog is a serotonin, norepinephrine reuptake inhibitor (SNRI).

55. A method of decreasing proinflammatory cytokine secretion or production in a patient, said method comprising administering to a patient an SSRI and a glucocorticoid receptor modulator simultaneously or within 14 days of each other in amounts sufficient *in vivo* to decrease proinflammatory cytokine secretion or production in said patient.

56. A method for treating a patient diagnosed with or at risk of developing an immunoinflammatory disorder, said method comprising administering to the patient an SSRI and a glucocorticoid receptor modulator simultaneously or within 14 days of each other in amounts sufficient to treat said patient.

57. The method of claim 56, wherein said immunoinflammatory disorder is rheumatoid arthritis, Crohn's disease, ulcerative colitis, asthma, chronic obstructive pulmonary disease, polymyalgia rheumatica, giant cell arteritis, systemic lupus erythematosus, atopic dermatitis, multiple sclerosis, myasthenia gravis, psoriasis, ankylosing spondylitis, cirrhosis, or psoriatic arthritis.

58. The method of claim 56, wherein said SSRI is cericlamine, citalopram, clovoxamine, cyanodothiepin, dapoxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, indalpine, indeloxazine, litoxetine, milnacipran, paroxetine, sertraline, tametraline, viqualine, or zimeldine.

59. The method of claim 56, wherein said SSRI analog is a serotonin, norepinephrine reuptake inhibitor (SNRI).

60. The composition of claim 56, wherein said SNRI is venlafaxine, duloxetine, or 4-(2-fluorophenyl)-6-methyl-2-piperazinothieno [2,3-d] pyrimidine.

61. The method of claim 56, further comprising administering to said patient a COX-2 inhibitor, NSAID, corticosteroid, small molecule immunomodulator, DMARD, biologic, xanthine, anticholinergic compound, beta receptor agonist, bronchodilator, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid, or 5-amino salicylic acid.

62. The method of claim 56, wherein said SSRI and said glucocorticoid receptor modulator are administered within 10 days of each other.

63. The method of claim 62, wherein said SSRI and said glucocorticoid receptor modulator are administered within five days of each other.

64. The method of claim 63, wherein said SSRI and said glucocorticoid receptor modulator are administered within twenty-four hours of each other.

65. The method of claim 64, wherein said SSRI and said glucocorticoid receptor modulator are administered simultaneously.

66. A pharmaceutical composition comprising (i) an SSRI or analog thereof and (ii) a second compound selected from the group consisting of a xanthine, anticholinergic compound, beta receptor agonist, bronchodilator, biologic, NSAID, DMARD, COX-2 inhibitor, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid, and 5-amino salicylic acid.

67. The composition of claim 66, wherein said NSAID is ibuprofen, diclofenac, or naproxen.

68. The composition of claim 66, wherein said COX-2 inhibitor is rofecoxib, celecoxib, valdecoxib, or lumiracoxib.

69. The composition of claim 66, wherein said biologic is adalimumab, etanercept, or infliximab.

70. The composition of claim 66, wherein said DMARD is methotrexate or leflunomide.

71. The composition of claim 66, wherein said xanthine is theophylline.

72. The composition of claim 66, wherein said anticholinergic compound is ipratropium or tiotropium.

73. The composition of claim 66, wherein said beta receptor agonist is ibutero1 sulfate, bitoltero1 mesy1ate, epinephrine, formoterol fumarate, isoproteronol, levalbutero1 hydrochloride, metaproterenol sulfate, pirbutero1 scetate, salmeterol xinafoate, or terbutaline.

74. The composition of claim 66, wherein said non-steroidal calcineurin inhibitor is cyclosporine, tacrolimus, pimecrolimus, or ISAtx247.

75. The composition of claim 66, wherein said vitamin D analog is calcipotriene or calcipotriol.

76. The composition of claim 66, wherein said psoralen is methoxsalen.

77. The composition of claim 66, wherein said retinoid is acitretin or tazoretene.

78. The composition of claim 66, wherein said small molecule immunomodulator is VX 702, SCIO 469, doramapimod, RO 30201195, SCIO 323, DPC 333, pranalcasan, mycophenolate, or merimepodib.

79. The composition of claim 66, wherein said SSRI analog is a serotonin, norepinephrine reuptake inhibitor (SNRI).

80. The composition of claim 79, wherein said SNRI is venlafaxine, duloxetine, or 4-(2-fluorophenyl)-6-methyl-2-piperazinothieno [2,3-d] pyrimidine.

81. A method for suppressing secretion of one or more proinflammatory cytokines in a patient in need thereof, said method comprising administering to the patient (i) an SSRI and (ii) a second compound selected from the group consisting

of a xanthine, anticholinergic compound, small molecule immunomodulator, biologic, NSAID, DMARD, COX-2 inhibitor, beta receptor agonist, bronchodilator, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid, and 5-amino salicylic acid in amounts sufficient *in vivo* to decrease proinflammatory cytokine secretion or production in said patient.

82. A kit, comprising:

- (i) a composition comprising an SSRI or SNRI and a corticosteroid; and
- (ii) instructions for administering said composition to a patient diagnosed with or at risk of developing an immunoinflammatory disorder.

83. A kit, comprising:

- (i) an SSRI or SNRI;
- (ii) a corticosteroid; and
- (iii) instructions for systemically administering said SSRI and said corticosteroid to a patient diagnosed with or at risk of developing an immunoinflammatory disorder.

84. A kit comprising (i) an SSRI or SNRI and (ii) instructions for administering said SSRI and a corticosteroid to a patient diagnosed with an immunoinflammatory disorder.

85. A kit, comprising:

- (i) an SSRI or SNRI;
- (ii) a second compound selected from the group consisting of a glucocorticoid receptor modulator, xanthine, anticholinergic compound, biologic, NSAID, DMARD, COX-2 inhibitor, beta receptor agonist, bronchodilator, non-

steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid, and 5-amino salicylic acid; and

(iii) instructions for administering said SSRI and said second compound to a patient diagnosed with or at risk of developing an immunoinflammatory disorder.

86. A method for identifying combinations of compounds useful for suppressing the secretion of proinflammatory cytokines in a patient in need of such treatment, said method comprising the steps of:

(a) contacting cells *in vitro* with an SSRI or SNRI and a candidate compound; and

(b) determining whether the combination of said SSRI and said candidate compound reduces cytokine levels in blood cells stimulated to secrete the cytokines relative to cells contacted with said SSRI but not contacted with said candidate compound or cells contacted with said candidate compound but not with said SSRI, wherein a reduction of said cytokine levels identifies said combination as a combination that is useful for treating a patient in need of such treatment.